

## REMARKS

Claims 1, 3, 5-7, 9, and 11-29 are pending in the instant application, once this amendment is entered. Claims 1, 2, 5-7, 9, and 11-21 are amended mainly for clarity, without prejudice or disclaimer of any previously claimed subject matter. Applicants respectfully submit that there is no new matter introduced.

Applicants have added new claims 22 to 29. Support for these new claims can be found in Table 1 on pages 22 to 25 of the application as originally filed. It is submitted that the new claims are fully supported in the original specification, and no new matter has been introduced.

### A. The Rejection under 35 U.S.C. § 112

The Office Action rejects claims 1, 3, 5-7, 9 and 11-21 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action alleges that “the insertion of ‘optionally’ in claim 1 in the definition of R is deemed as new matter.” Applicants respectfully traverse.

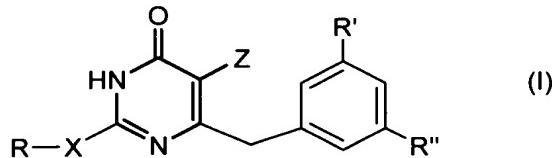
As disclosed in the original specification, it is clearly indicated that the alkyl and cycloalkyl in the definition of R optionally contains one or more heteroatoms selected from O, S, or N. Among the compounds as shown in Table 1 on pages 22 to 25 of the application as originally filed, about 148 compounds have R as alkyl or cycloalkyl. However, only seven of them contain a heteroatom in the chain and the remaining 141 compounds do not contain any heteroatom at all as parts of their alkyl or cycloalkyl groups as R. Thus, Applicants respectfully request that this new matter rejection be reconsidered and withdrawn.

### B. The Rejection under 35 U.S.C. § 103(a)

Claims 1, 3, 5-7, 9 and 11-21 are rejected under 35 U.S.C 103(a) as allegedly being unpatentable over WO 96/10565 (hereinafter, the ‘565 publication). The Office Action alleges that the compounds of the instant claims are homologs of the compounds disclosed in the ‘565 publication, and that “homologs and compounds that differ only by CH<sub>3</sub> vs. H are not deemed patentably distinct absent evidence of superior or unexpected properties.” Citing *In re Wood* 199 USPQ 137; *In re Lohr* 137 USPQ 548. Applicants respectfully traverse.

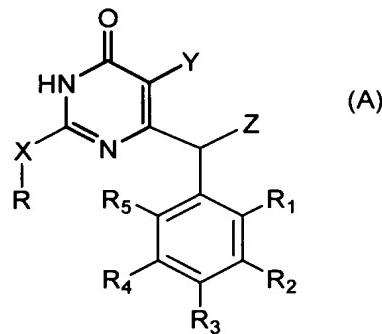
The Court in *In re Henze* defines a homologous series as “a family of chemically related compounds, the composition of which varies from member to member by CH<sub>2</sub>.” 85 USPQ at 264 (citing *In re Loring Coes, Jr.*, 173 F.2d 1012, 81 USPQ. 369 (CCPA 1949)). The Court held that the claimed compound, 5-isopropoxymethyl-5-phenylhydantoin, was obvious in view of the prior art compound, 5-ethoxymethyl-5-phenylhydantoin, which differed from the claimed compound by a CH<sub>2</sub> group. 85 USPQ at 263. Similarly, in *In re Hass*, the Court held that the claimed compound, 1-phenyl-2-nitro-1-butene, was obvious in view of 2 adjacent lower homologues disclosed by the prior art: 1-phenyl-2-nitro-1-propene and 1-phenyl-2-nitro-1-ethene. 60 USPQ. at 546. Each member of the homologous series was distinguished by a single CH<sub>2</sub> group. Thus, in both *Hass* and *Henze*, obviousness was found where the claimed compound was distinguished from the prior art compound only by the adjacent addition of a CH<sub>2</sub> group.

However, the compounds in claims 3, 14, and 15 are not homologs of the compounds disclosed in the ‘565 publication. The Office Action neglects other significant differences between the compounds in these claims and the compounds disclosed in the ‘565 publication. The compounds disclosed in the ‘565 publication have Formula I:



wherein X is O or S; R is C<sub>1-4</sub> alkyl or C<sub>5-6</sub> cycloalkyl; and R', R'', and Z are each independently H or C<sub>1-4</sub> alkyl.

In contrast, the compounds in claims 3, 14, and 15 of the instant application have the structures of formula A:



wherein at least one of R<sup>1</sup> and R<sup>5</sup> is nitro, chloro, or fluoro. Thus, the compounds of claims 3, 14, and 15 are not homologs of the compounds of Formula I as disclosed in the ‘565 publication. The compounds of claims 3, 14, and 15 have different substitution pattern on the aromatic ring, from the compounds disclosed in the ‘565 publication. The compounds of claims 3, 14, and 15 have at least one substitution at R<sup>1</sup> and/or R<sup>5</sup> (such as nitro, chloro or fluoro), whereas the compounds in the ‘565 publication do not have any substitution on either R<sup>1</sup> or R<sup>5</sup>. For at least this reason, Applicants respectfully request that this rejection of claims 3, 14, and 15 be reconsidered and withdrawn.

With regard to the rejection of claims 1, 5-7, 9, 11-13, and 16-21 under 35 U.S.C. § 103(a), the U.S. Supreme Court has recently acknowledged the importance of identifying “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does” in determining obviousness. Citing *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). The Court noted that the analysis supporting a rejection under 35 U.S.C. 103(a) should be made explicit, and that “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” 127 S. Ct at 1741. Further, the Federal Circuit has recently reviewed the requirements for making a *prima facie* case of obviousness for chemical compositions in view of *KSR*. See *Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc., v. Alphapharm Pty., Ltd. and Genpharm, Inc.*, 2007 U.S. App. Lexis 15439. “In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of ‘adequate support in the prior art’ for the change in the structure.” *Id* at 9 (citing *In re Grabiak*, 769 F.2d 729, 731-732 (Fed. Cir. 1985). A showing must be made that the “prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.” *Id* at 9 (citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Dillon* 919 F.2d 688 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984). Thus, in cases involving new chemical compounds, it is necessary to identify “some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.” 2007 U.S. App. Lexis 15439 at 10.

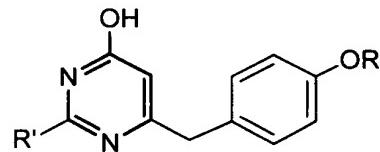
Applicants respectfully submit that the Office Action has not provided a reason why

one of ordinary skill in the art would modify the teachings of the '565 publication to arrive at the compounds of the instant claims. In particular, no reason has been articulated as to why the skilled artisan would substitute hydrogen on the methylene linkage of the compounds disclosed in the 565 publication, with one of the substituents recited in claim 1. Because the Office Action has not met this burden, the instant claims are not obvious. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Furthermore, the compounds of the instant claims show superior biological activity in comparison with those disclosed in the '565 publication. The best compound in the '565 publication exhibits an EC<sub>50</sub> of 0.6 μM and SI of >506 (Table 4 on page 17). In contrast, the instant application discloses over three dozens of compounds that have EC<sub>50</sub> values of no greater than 0.06 μM, or at least ten times potent than the best compound in the '565 publication. One of these potent compounds is MC1047+ shown in Table 2 on page 30 of the specification originally filed. MC1047+ compound having methyl as Z has an EC<sub>50</sub> of 0.002 μM, which is three-hundred fold more potent than the most potent compound disclosed in the '565 publication. MC1047+ compound also exhibits a superior therapeutic index as measured by its SI value. MC1047+ compound has an SI of >100,000, which is about 500 fold higher than the SI value of the best compound disclosed in the '565 publication. The superior biological activity of MC1047+ compound and others in the instant claims could not have been predicted from the teachings of the '565 publication, and provide objective evidence of non-obviousness of the instant claims. Therefore, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

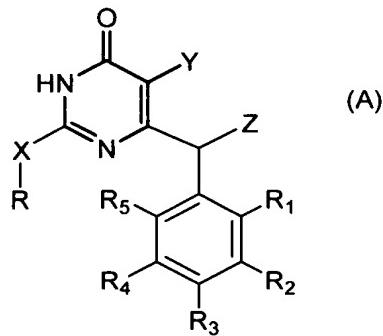
In the Office Action, claims 1, 3, 5-7, 9 and 11-21 are also rejected under 35 U.S.C 103(a) as allegedly being unpatentable over Aroyan et al. (Arm. Khim. Zh. 24(2):161-166, 1971) (hereinafter, Aroyan). The Office Action alleges that the compounds of the instant claims are homologs of the compounds disclosed by Aroyan, and that "homologs and compounds that differ only by CH<sub>3</sub> vs. H are not deemed patentably distinct absent evidence of superior or unexpected properties." Citing *In re Wood* 199 USPQ 137; *In re Lohr* 137 USPQ 548.

Aroyan discloses substituted (4-alkoxy-benzyl)pyrimidines of the formula:



wherein R is CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>; and R' is SH, NH<sub>2</sub>, CH<sub>3</sub>, or CH<sub>2</sub>OH.

As discussed hereinabove, the compounds of claims 3, 14, and 15 in the instant application have the structures of formula A:



wherein at least one of R<sup>1</sup> and R<sup>5</sup> is nitro, chloro, or fluoro. Thus, the compounds of claims 3, 14, and 15 are not homologs of the compounds disclosed by Aroyan. The compounds of claims 3, 14, and 15 have different substitution pattern on the aromatic ring, from the compounds disclosed by Aroyan. The compounds of claims 3, 14, and 15 have at least one substitution at R<sup>1</sup> and/or R<sup>5</sup> (such as nitro, chloro or fluoro), whereas the compounds disclosed by Aroyan do not have any substitution on either R<sup>1</sup> or R<sup>5</sup>. For at least this reason, Applicants respectfully request that this rejection of claims 3, 14, and 15 be reconsidered and withdrawn.

With regard to the rejection of claims 1, 5-7, 9, 11-13, and 16-21 under 35 U.S.C. § 103(a), the Office Action, as discussed hereinabove, has not provided a reason why one of ordinary skill in the art would modify Aroyan's teachings to arrive at the compounds of the instant claims. In particular, no reason has been articulated as to why the skilled artisan would substitute hydrogen on the methylene linkage of the compounds disclosed by Aroyan, with one of the substituents recited in claim 1. Because the Office Action has not met this burden, the instant claims are not obvious. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

C. The Double Patenting Rejection

Claims 1-3 and 5 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-23 of Applicants' prior U.S. Patent No. 6,545,007. Applicants request deferral of this issue until an indication of allowable subject matter in the instant application.

Claims 1-3, 5-7, 9 and 11-21 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17-25 and 30-46 of copending Application No. 10/350,772. Applicants request deferral of this issue until an indication of allowable subject matter in each application.

Claims 1-3, 5-7, 9 and 11-21 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 and 29 of copending Application No. 11/327,672. Applicants request deferral of this issue until an indication of allowable subject matter in each application.

Claims 1-3, 5-7, and 9-12 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 and 37-80 of copending Application No. 10/833,601. Applicants request deferral of this issue until an indication of allowable subject matter in each application.

## SUMMARY

It is submitted that this amendment meets the requirements of 37 C.F.R. §1.116(b) for entry of amendments after final rejection. Entry of this amendment is therefore respectfully requested. It is also submitted that the foregoing amendment and argument addresses all grounds of objection and rejection, and that this application is in order for allowance.

Should the Examiner believe that prosecution of this application might be expedited by further discussion of any remaining issue, the Examiner is cordially invited to contact the undersigned representative of Applicants, Dale L. Rieger, Ph.D., by phone at (858) 314-1200 or by email at [drieger@jonesday.com](mailto:drieger@jonesday.com).

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-3013 and please credit any excess fees to such deposit account.

Respectfully submitted,

Dated: August 21, 2007

By:   
Dale L. Rieger, Ph.D.  
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